IJAE
Vol. 120, n. 1 (Supplement): 52, 2015
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Critical role of phosphodiesterase 2A in congenital heart disease

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cAMP and cGMP levels are regulated in a highly specific and stimulus-dependent manner by cyclic nucleotide degrading phosphodiesterases (PDEs). Among the different PDEs, PDE2A is unique because it responds to elevated cGMP levels increasing its cAMP hydrolytic activity. PDE2A is essential for mouse development and Pde2A null mice die in utero (1). Pde2A$^{-/-}$ embryos display a nuchal edema which is associated with congenital heart defects in other mouse models (2). To investigate if the absence of PDE2A is associated with heart defects, macroscopical and microscopical observations of hearts isolated from Pde2A$^{-/-}$ E14.5 embryos were performed. Pde2A$^{-/-}$ hearts appeared enlarged compared to the wild type counterparts and displayed interventricular septum defect, hypertrabeculation, myocardial wall defects and atrial trabeculae loss. Increased apoptosis was detected in specific areas of Pde2A$^{-/-}$ hearts. Compromised expression pattern of critical genes involved in heart development (T-box genes) was observed. RT-PCR analysis revealed that Tbx1, Tbx2, Tbx18 and Tbx20 expression was significantly down-regulated in hearts from Pde2A$^{-/-}$ mice. To investigate whether cAMP might regulate T-box gene expression, fetal cardiomyocytes were treated with a PDE2A inhibitor (EHNA) and the β-adrenergic agonist Isoproterenol (Iso). T-box gene expression was down-regulated in cardiomyocytes treated with EHNA and Iso. Taken together these data suggest that PDE2A activity cannnot be replaced by other phosphodiesterases and its specific function could be the modulation of T-box gene expression during embryonic development. To our knowledge, this is the first time that the genetic deletion of a phosphodiesterase is associated with the establishment of congenital heart defect.

References

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Keywords
Pde2A. Congenital heart disease.